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Ultrasound Assisted Cooling Crystallization of Lactose Monohydrate

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***Abstract*—**α-lactose monohydrate is widely used in the pharmaceutical industries as an inactive substance that acts as a vehicle or a medium for a drug or other active substance. It is a byproduct of dairy industries, and the recovery of lactose from whey not only boosts the improvement of the economics of whey utilization but also causes a reduction in pollution as lactose recovery can reduce the BOD of whey by more than 80%. In the present study, levels of process parameters were kept as initial lactose concentration (30-50% w/w), sonication amplitude (20-40%), sonication time (2-6 hours), and crystallization temperature (10-20 °C) for the recovery of lactose in ultrasound assisted cooling crystallization. In comparison with cooling crystallization, the use of ultrasound enhanced the lactose recovery by 39.17% (w/w). The parameters were optimized for the lactose recovery using Taguchi Method. The optimum conditions found were initial lactose concentration at level 3 (50% w/w), amplitude of sonication at level 2 (40%), the sonication time at level 3 (6 hours), and crystallization temperature at level 1 (10 °C). The maximum recovery was found to be 85.85% at the optimum conditions. Sonication time and the initial lactose concentration were found to be significant parameters for the lactose recovery.

***Keywords*—**Crystallization, Taguchi method, ultrasound, lactose.

I. Introduction

CRYSTALLIZATION is the most common method used to produce pharmaceutical drug materials. The production of crystals with well-defined physical and chemical properties is a critical problem for the industries [1]. Lactose is a very important pharmaceutical ingredient used as an excipient in dry powder inhalers (DPIs). The drug particles used in DPIs should possess certain desirable properties like hydrodynamics diameter in the range of 2-6 μm and particle crystallinity to ensure formulation stability [2].

In the dairy industries, lactose is produced from whey which is by-products from the production of cheese/Paneer. Extracting the lactose from whey has dual benefits. The economy of whey utilization is increased and at the same time, it reduces pollution as lactose extraction from whey can reduce the biochemical oxygen demand by more than 80% [1]. The conventional cooling lactose manufacturing process provides a minimal avenue for fine control of crystal size required for DPIs. The milling and micronization process which are being currently used to produce desired lactose crystal size adversely impacts powder flowability and lactose crystal structure. Thus, there is a need to produce lactose crystals of desired shape and size without further processing. The lactose crystallization during refining typically generates a large number of small crystals but having a low recovery [3].

The problem associated with the conventional cooling lactose crystallization is the large metastable zone width and also high induction time (the time elapsed between the creation of supersaturation and appearance of crystals) [4]. These two factors can be controlled with the help of ultrasound during the crystallization. The application of ultrasound reduces both induction time and metastable zone width at low supersaturations. The use of ultrasound in crystallization provides the nucleation energy and therefore it reduces the induction time which affects finally on the recovery of lactose. Hence, ultrasound can replace the seeding in conventional cooling crystallization. Also, ultrasound improves the quality of crystals by reducing agglomeration and changing crystal habit [5]. Therefore, the aim of the present work is to use the ultrasound in the cooling crystallization to enhance the yield of the lactose from whey and to optimize this process to give maximum response for the recovery of lactose using Taguchi orthogonal array method.

A. Taguchi Approach to Parameter Design

The Taguchi method is a systematic statistical method to determine the optimum design parameters for performance and cost by obtaining the best combination of process parameters. In this method, orthogonal arrays from the design of experiments are used to study a large number of parameters with a small number of experiments [6]. Taguchi has provided tabulated sets of standard orthogonal arrays and corresponding linear graphs to fit specific projects [7]. A typical L_9 (3^4) orthogonal array is shown in Table I. According to these conditions, experiments are needed to be carried out. After this, Taguchi method uses a statistical measure of performance called 'Signal-to-noise' ratio (S/N ratio). The level total table is generated from Signal-to-noise value, and the optimum condition is decided based on the highest value of Signal-to-noise in a level total table. Further, to find out the most significant parameter which has the highest effect on the performance characteristic, analysis of variance (ANOVA) is used.

II. Experimental

A. Materials

α-lactose monohydrate (99% purity, Finar chemicals limited, Ahmedabad, India) is used as received. Millipore water was used in all experiments.

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TABLE I
L_9 (3^4) ORTHOGONAL ARRAY

	A	B	C	D
1	1	1	1	1
2	1	2	2	2
3	1	3	3	3
4	2	1	2	3
5	2	2	3	1
6	2	3	1	2
7	3	1	3	2
8	3	2	1	3
9	3	3	2	1

B. Experimental Procedure

A solution of α-lactose monohydrate was prepared by dissolving the predetermined quantity of α-lactose monohydrate in 100 ml water over a magnetic stirrer at a temperature of 80 ^{0}C (because at any temperature over 75 ^{0}C, the mobility of α-lactose monohydrate increases) and at 500 rpm. The solution was allowed to stand over the magnetic stirrer at the above-mentioned conditions for the duration of 30 minutes to ensure complete mixing of α-lactose monohydrate in water. The solution was then filtered to ensure that no undissolved particles of α-lactose monohydrate were present in the solution. This filtered solution is again placed over the magnetic stirrer at same conditions for the duration of 45 minutes. This solution is then transferred to a double-jacketed glass crystallizer connected with a recirculating cooling bath (Thermo scientific, India) and placed over a magnetic stirrer which is maintained at 500 rpm. Also, a sonication probe is dip in solution contained in the double-jacketed crystallizer for the application of ultrasound. The crystals are allowed to form for a pre-decided number of hours, and the solution of crystals in water is filtered using Whatmann no. 41 and the crystals recovered were dried in vacuum oven (Aqua scientific instruments, Surat, India) which is then weighed, and the yield was calculated. Sonication was applied for 59 seconds on and then off for 59 seconds and this was continued till the pre-decided crystallization time.

The operating parameters; viz: initial lactose concentration (30-50% w/w), sonication amplitude (20-40%), crystallization time (2-6 hours), and crystallization temperature (10-20 ^{0}C) were varied to obtain the lactose.

C. Design of Experiments

Optimization of parameters of ultrasound-assisted cooling crystallization is important in order to achieve a high recovery of lactose. There are many operational parameters which can affect the ultrasound-assisted cooling crystallization process and therefore, four different factors; viz initial lactose concentration (30- 50% w/w), sonication amplitude (20-60%), crystallization time (2-6 hours), and crystallization temperature (10-20 ^{o}C) were investigated for the lactose recovery at three levels. The factors and their values are shown in Table II. According to this, the L9-orthogonal array was prepared and is shown in Table III to carry out the experiments. The yield of lactose was considered as Taguchi array response and is obtained using ultrasound assisted cooling crystallization.

There are several S/N ratio which are available and dependent on the type of quality characteristics (responses) [8]. These S/N ratios are "lower is the best", "higher is the best", and "nominal is best quality" characteristic. The present study aimed to higher lactose recovery as the quality characteristic, "the higher is the best" S/N ratio was selected as shown below.

$$\left[\frac{S}{N}\right]_{HB} = -10\log\left(\frac{1}{n}\right)\sum_i^n \frac{1}{y_i^2} \quad (1)$$

The ANOVA procedure was used to determine the percentage contribution of each of the parameters that were studied. The equations that were used to perform the ANOVA calculations are selected according to Patel and Murthy [8].

TABLE II
PARAMETERS AND THEIR LEVELS IN THE EXPERIMENTAL DESIGN

Level	Parameter A (initial lactose concentration, %w/w)	Parameter B (sonication amplitude)	Parameter C (crystallization time, min)	Parameter D (crystallization temperature, ^{0}C)
1	30	20	2	10
2	40	40	4	15
3	50	60	6	20

TABLE III
L_9-ORTHOGONAL ARRAY AND RESPONSE VALUES (PERCENTAGE LACTOSE YIELD)

Run	A	B	C	D	Response 1	Response 2	S/N ratio
1	1	1	1	1	4.08	4.36	12.51
2	1	2	2	2	4.02	10.6	14.53
3	1	3	3	3	5.5	5.5	14.81
4	2	1	2	3	9.96	3.37	13.10
5	2	2	3	1	62.7	71.4	36.47
6	2	3	1	2	16.9	4.01	14.85
7	3	1	3	2	78.29	77.3	37.82
8	3	2	1	3	48.12	67.97	34.89
9	3	3	2	1	76.18	75.71	37.61

III. RESULTS AND DISCUSSIONS

A. Effect of Supersaturation

Fig. 1 shows the effect of ultrasound on percentage yield in cooling crystallization. It can be observed that conventional cooling crystallization required 8 hours to crystallizethe lactose with 62.38% w/w, whereas cooling crystallization in the presence of ultrasound required 4 hours to obtain 68.08% w/w). It is also observed that, at lower supersaturation, no crystals of lactose were observed in conventional cooling crystallization, whereas in the presence of ultrasound, lactose was crystallized with 4.01%w/w. It is obvious that the higher superstation will give a higher yield of lactose as shown in Fig. 1. Ultrasound is known to decrease the induction time and metastable zone width in the crystallization, and therefore, it enhances the yield in the crystallization process. Thereby, the enhancement in the percentage recovery was found to be 39.17% w/w at 2.65 supersaturation.

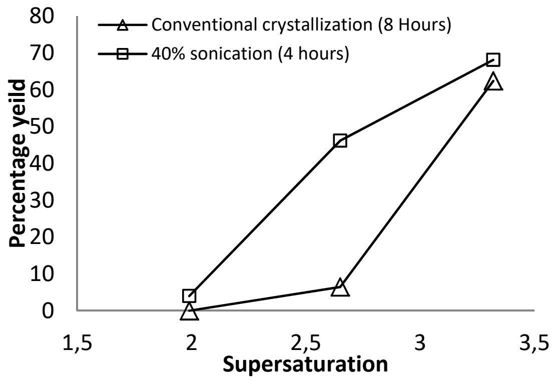

Fig. 1 Effect of ultrasound on percentage yield

B. Optimization of Process Parameters

The percentage lactose recovery was obtained by performing the experiments according to the L9-orthogonal array and the 'S/N ratio' was calculated for each combination of the levels of factors. Based on this, a level total table was prepared to obtain the total value for each level of factors (Table IV).

TABLE IV
TOTAL S/N RATIOS (HIGHER IS THE BEST)

	Parameters			
Level	**A**	**B**	**C**	**D**
1	41.84	63.42	62.25	86.59
2	64.42	85.89	65.24	67.19
3	110.32	67.26	89.10	62.80

Table IV shows the highest value of levels of each factor. Therefore, the best combination of factors and their levels were found as factor A at level three, factor B at level two, factor C at level three, and factor D at level one. So the optimum condition in ultrasound assisted cooling crystallization to obtain the maximum recovery of lactose is found as initial lactose concentration at level 3 (50% w/w), amplitude of sonication at level 2 (40%), time of crystallization at level 3 (6 hours), and the temperature of crystallization at level 1 (10 ^{0}C). At these optimized conditions, an experiment was carried out for lactose recovery, and the recovery of lactose was found to be 85.85% w/w.

Moreover, to find out the significance of each process parameter on the lactose recovery, ANOVA was performed, and their values are shown in Table V. The significance of the factors on the lactose recovery is found by comparing the factor variances. It can be observed that initial lactose concentration is found more significant with 70.02% as compared to other parameters. The larger the contribution of the factor to the total variation, larger is the ability of a factor to influence S/N ratio. Based on the F-test and percentage contribution, factors that are influencing towards the lactose recovery have been found in the following order: initial lactose concentration > time of crystallization > temperature of crystallization > amplitude of sonication.

Scanning electron microscope (SEM) of the pure lactose crystals and lactose crystals recovered at optimum conditions (as per Taguchi method) are shown in Fig. 2. It can be seen that not much change was observed in the morphology of the raw lactose crystals and the lactose crystals obtained at optimum condition. However, the size of the lactose at optimum condition is drastically reduced. The reduction in the crystal size is mainly attributed to the presence of ultrasound during the cooling crystallization.

TABLE V
ANOVA

Factor	Sum of squares	Degree of freedom	Fp (Variance ratio)	% contribution
A	811.79	2	8.43	70.02
B	96.30	2	1.00	8.31
C	144.38	2	1.50	12.45
D	106.83	2	1.11	9.22
Error	0	0	-	-
Total	1159.29	8	-	-
Pooled Error	96.30	2	-	-

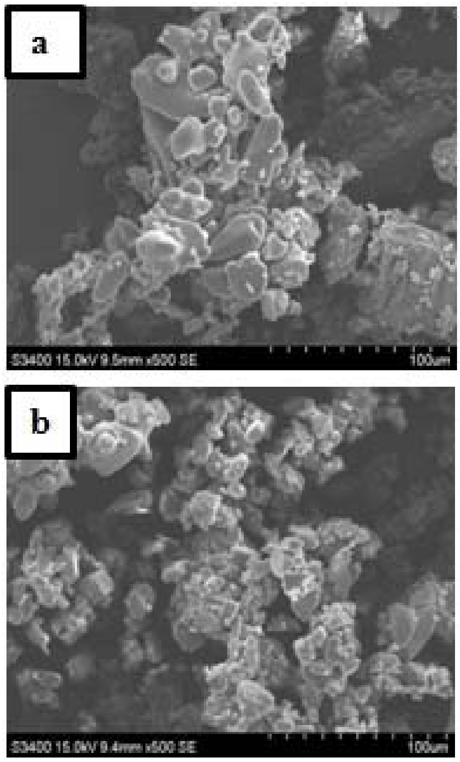

Fig. 2 SEM images of lactose crystals (a) Raw lactose, (b) Lactose obtained at optimum condition

IV. CONCLUSION

Best combination of factors and their levels in order to find out the maximum lactose recovery was found using Taguchi design of experiments in the ultrasound-assisted cooling crystallization of α-lactose monohydrate. The L_9-orthogonal array method of Taguchi was used and the optimum conditions were found for ultrasound assisted cooling crystallization is as initial lactose concentration at level 3

(50% w/w), amplitude of sonication at level 2 (40%), the crystallization time at level 3 (6 hours), and crystallization temperature at level 1 (10 ^{0}C). The maximum recovery was found to be 85.85% at the optimum condition. In comparison with cooling crystallization, the use of ultrasound enhanced the lactose recovery by 39.17% w/w.

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